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Applicant(s): **Summers et al.**

Docket No. **2991/1/US**

Serial No.	Filing Date	Examiner	Group Art Unit
08/954,954	**10/21/1997**	**Kemmerer**	**1646**

Invention: **Novel Erythropoietin Receptor Agonists**

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Case C-2991/1

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE APPLICATION OF:	
Summers et al.	GROUP ART UNIT: 1646
SERIAL NUMBER: 08/954,954	EXAMINER: Elizabeth Kemmerer
FILED: October 21,1997	DATE: November 09, 2001

TITLE: Novel Erythropoietin Receptor Agonists

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APPEAL BRIEF FOR SUMMERS ET AL.

Honarable Commissioner of Patent
Washington D.C. 20231

Appellant appeals from the final rejection dated November 07, 1999 of claims 1-14 of this application.

The fees required under § 1.17(r), and any required petition for extension of time for filing this brief and fees therefor, are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief is transmitted in triplicate (37 C.F.R. 1.192(a)).

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02 FC:120 320.00 CH
03 FC:121 280.00 CH

Real Party In Interest

The subject application is owned by G.D. Searle and Company, a wholly-owned subsidiary of Pharmacia Corp, Peapack New Jersey.

Related Appeals and Interferences

No other appeals or interferences are known to Appellant, which will directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

Status of Claims

Claims 1-14 are currently pending, claims 15-22 having been withdrawn to a restriction requirement. Claims 1-14 stand finally rejected under 35 U.S.C. § 103(a). Claims 1-14 are under appeal. Claims 1-14 as amended are shown in Appendix 1.

Status of Amendments

Applicants amended claim 4 in the Amendment filed 13 September 2000, under 37 C.F.R. § 1.114, which was entered.

Applicants filed an Amendment After Final under 37 C.F.R. § 1.116 on May 04, 2001 and a Notice of Appeal on May 07, 2001, which was received by the USPTO on May 10, 2000. The Examiner failed to provide an Advisory Action in response to the

Amendment After Final under 37 C.F.R. § 1.116. Pursuant to the filing of this brief Applicants request that the proposed amendment be entered.

The Examiner indicated in the Office Action of 07 November 2000 that the rejection under 35 U.S.C. § 112, second paragraph is withdrawn.

Summary of Invention

The invention relates to circulary permuted EPO receptor agonists, nucleic acids encoding such, compositions comprising such, recombinant expression of such, and methods of treating patients using the protein as the active agent. Since the modification of the EPO ligand represents a rearrangement of the molecule, neither the function, nor the desirability of such was apparent prior to the work in the present application. These EPO receptor agonists retain one or more activities of native EPO ligand and may also show improved hematopoietic cell-stimulating activity and/or an improved activity profile which may include reduction of undesirable biological activities associated with native EPO ligand and/or have improved physical properties which may include increased solubility, stability and refold efficiency.

Issues

Issue 1 - Whether claims 1, 5, and 10-14 are patentable under 35 U.S.C. § 103(a), over Pastan et al. (U.S. Patent 5,635,599) taken in view of Lin (U.S. 4,703,008).

Issue 2 - Whether claims 1-4 and 6-9 are patentable under 35 U.S.C. § 103(a), over Pastan et al. (U.S. Patent 5,635,599) taken in view of Lin (U.S. 4,703,008), Chaudary et al., (1989, *Nature* 339:394-397) and Cousens et al. (U.S. Patent 4,751,180).

Grouping of Claims

For each ground of rejection which appellant contests herein which applies to more than one claim, such additional claims, to the extent separately identified and argued below, do not stand or fall together.

The Examiner's Rationale

In the Office Action dated October 13, 1998 the Examiner rejected Claims 1, 5, and 10-14 under 35 U.S.C. § 103(a) as allegedly being obvious over Pastan *et al.* (U.S. Patent 5,635,599) taken in view of Lin (4,703,008).

> *Pastan et al. teaches growth factor agonist polypeptides and nucleic acids encoding same, wherein the N-terminus is joined to the C-terminus directly or through a linker capable of joining the N-terminus to the C-terminus and having a new C- and N-termini in the middle of the polypeptide. Pastan also teaches that erythropoietin (EPO) is amenable to this procedure, which they term "circular permutation. Pastan et al. Teach a method of recombinantly producing the circularly permuted ligand. Pastan also teach pharmaceutical compositions comprising the circularly permuted growth factor, complementary growth factors, and a pharmaceutically acceptable carrier.*
>
> *Pastan et al do not disclose a working example of circularly permuted EPO, nor do they disclose a sequence of EPO. However, human EPO had been previously characterized. Pastan et al. disclose that a good choice for an "opening site" is where substitution of amino acids is tolerated. Lin in Figure 9 align human and monkey sequences. Both are functional. Differences*

> *occur at amino acid positions 25, 27, 30, 32, 80, 82, 88, 116, and 121. This suggests that an opening site would be tolerated in a circularly permuted EPO molecule at these sites. Lin also teaches pharmaceutical composition comprising EPO and a pharmaceutically acceptable carrier, and a method of stimulating the production of hematopoietic cells in a patient comprising administration of same.*
>
> *Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the circular permuted growth factors, DNA encoding same, methods of recombinantly producing same, and pharmaceutical compositions comprising same as taught by Pastan et al. and to modify that teaching by extending it to EPO disclosed by lin, with opening sites at 25, 27, 30, 32, 80, 82, 88, 116, or 121. A reasonable expectation of success is given by Pastan et al.'s disclosure that preferred opening open sites are those which can tolerate amino acid substitution and Lin's disclosure of substitution toleration at positions 25, 27, 30, 32, 80, 82, 88, 116, or 121. The motivation to do so is provided by Pastan et al. in their express suggestion to extend the teachings to EPO.*

In the Office Action dated April 29, 1999 the Examiner raises a new rejection of claims 1-4 and 6-9 under 35 U.S.C. § 103(a), as allegedly being obvious over Pastan et al. (U.S. Patent 5,635,599) taken in view of Lin (U.S. 4,703,008), Chaudary et al., (1989, *Nature* 339:394-397) and Cousens et al. (U.S. Patent 4,751,180).

> *Pastan et al. in view of Lin teach circularly permuteins embraced by claim 1, for Example. Neither reference teaches GlySer-rich linker sequences as required by claims 2-4 and 6-9.*

Chaudhary et al. disclose the use of a GlySer-rich linker for connecting antibody variable domains. Cousens et al., discloses that non-polar amino acids are useful for a flexible linker.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make circularly permuteins of EPO as taught by Pastan et al. in view of Lin, and to modify that combined teaching by using GlySer-rich flexible linkers between the two positions of the circular permuteins as taught by Chaudhary et al. and Cousens et al. with a reasonable expectation at successfully achieving a circular permutein with sufficient flexibility in the linker for the two positions of the circular permutein to fold favorably for retained function. The motivation to do so is provided by the disclosure of Chaudary et al. and Cousens et al. which disclose that the flexible linkers do not destroy activity.

Thus, the claimed invention as a whole was very clearly prima facie obvious over the prior art.

In the Office Action dated April 14, 2000 the Examiner Finally rejected under 35 U.S.C. § 103(a) claims 1, 5, and 10-14; and claims 1-4 and 6-9.

In the Office Action dated November 07, 2000 subsequent to the applicant's request for continued examination 37 C.F.R. § 1.114, the Examiner Finally rejected under 35 U.S.C. § 103(a) claims 1, 5, and 10-14; and claims 1-4 and 6-9 as set forth previously.

Argument

Issue 1 - Whether claims 1, 5, and 10-14 are patentable under 35 U.S.C. § 103(a), over Pastan et al. (U.S. Patent 5,635,599) taken in view of Lin (U.S. 4,703,008).

Appellants maintain the previous arguments set forth in traverse of this rejection that the Office has failed to establish a *prima facie* case of obviousness.

In the present case the prior art merely invites further experimentation, i.e., the present rejection is based upon the repeatedly rejected improper standard of ***obvious to try***. *In re Mercier*, 185 USPQ 774 (CCPA 1975); *Ex parte Old*, 229 USPQ 196 (BPAI 1985); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986); *In re Geiger*, 2 USPQ2d 176 (Fed. Cir. 1987); *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988); *In re O'Farrell*, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988).

As explained in *O'Farrell* at 1681, the admonition that ***obvious to try*** is not the standard under § 103 has been directed mainly at two kinds of error:

1. Varying all parameters or trying each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical, or no direction as to which of many possible choices is likely to be successful; and

2. Exploring a new technology or general approach that seemed to be a promising filed of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

The present situation is exactly the errors, that the Federal Circuit exhorted *In re O'Farrell* was an improper obvious to try situation and was not the standard of obviousness under 35 U.S.C. § 103(a).

First, it is imperative to review exactly what Pastan et al. discloses. Pastan et al. is limited to working examples disclosing only two circular permutation breakpoints (37-38 and 104-105) of IL-4 (Example 1) and these molecules in the context of a chimeric molecule with a cytotoxin (Example 2 & 4) or an antibody fragment (Fv) (Example 5). Only prophetic examples are disclosed for one circularly permuted form each of IL-2

(Example 5, column 25-26), G-CSF (Example 6, column 26) and GM-CSF (Example 6, column 26) are disclosed in '599. However, it is **not** shown that these IL-2, G-CSF, and GM-CSF molecules are properly folded or have any activity. Pastan et al. also lists a number of general options for the selection of "opening sites" in a protein (last paragraph of column 8 through first paragraph of column 9) including; a) that the opening site is in a region that lacks structure; b) that the opening site is at a residue that can be substituted by another amino acid; c) that the opening site is at a residue that can be modified (ie. glycosylated); or d) that the opening site is in a non-conserved region amongst a related family of proteins. Of these options, Pastan et al. only teaches that in the case of IL-4 that residues 38 and 105 are potential glycosylation sites and that circular permutation at these two breakpoints results in molecules that have reduced bioactivity relative to native IL-4. There is no factual basis or experimental data provided by Pastan et al. supporting the generalization that opening sites can be made at a residue that can be substituted by another amino acid, that the opening site can be made in a region that lacks structure, or that the opening site is in a non-conserved region amongst a related family of proteins. In addition, clearly each one these possible options will result in different distinct subsets of breakpoints. Pastan et al. provides numerous possible paths to take, all of which would lead one skilled in the art in different directions. Pastan et al, merely suggests exploring a general approach, sets forth a series of options, and suggests trying each of the numerous possible choices until one arrives at a successful result. Clearly, one skilled in the art is left guessing, which path to follow. O'Farrell stands for the proposition that the prior art must set forth what the critical parameters are. Pastan fails to indicate which parameters are critical for determining breakpoints in EPO. One skilled in the art is merely presented with a list of parameters to explore to determine what is critical, thereby constituting undue experimentation, which is an improper standard for a determination of obviousness. The Federal Circuit sustained as correct a jury instruction that "[*r*]*eferences relied upon to support a rejection for obviousness must provide an enabling disclosure*." (Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 1550, 13 USPQ2d 1301, 1304 (Fed. Cir> 1989). If a reference discloses only a hypothetical chemical structure, and does not enable is production, the Federal Circuit has indicated that the

disclosure of the references does not raise a question of obviousness. In *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.* 227 USPQ 657 (Fed. Cir. 1985) the Federal Circuit stated that:

> *[t]he test of whether a particular chemical compound described in the prior art may have been relied upon to show that the claimed subject matter at issue would have been obvious is whether the prior art provide an enabling disclosure with respect to the disclosed prior art compound."* 227 USPQ at 667, citing *In re* Donohue, 766 226 USPQ 619, 621 (Fed. Cir. 1985)

Based on evidence that the compound disclosed by the reference was merely a hypothetical structure, and that the reference in fact did not enable the production of the disclosed compound by one skilled in the art, then the cited prior art is not available as a reference and can not be properly combined with the remaining references to derive the claimed compound structure.

There are further fatal errors in the Offices *prima facie* case of obviousness. In the rejection the Office has focused on only one the options set forth by Pastan et al., ie. the opening site is at a residue that can be substituted by another amino acid. To support this argument the Office relies on Lin ('008) to provide a sequence homology alignment of two EPO species, human and cynomolgus monkey. The Office argues that the alignment of the two sequences shows that positions 25, 27, 30, 32, 80, 82, 88, 116, and 121 are non-conserved. The Office extends this argument to the notion that amino acid substitutions could be made at these positions. Therefore, the Office argues that making breakpoints at these positions would be obvious in view of the suggestion by Pastan. However, the disclosure of '008 does not teach individual sites at which amino acid substitutions can be made. The applicants respectfully submit that from this single alignment the Examiner has incorrectly concluded that, at any one of these single residue, amino acid substitutions can be made without effecting the bioactivity. At best, it can only be properly concluded that all of the fourteen amino acid differences at positions 25, 27, 30, 32, 80, 82, 88, 95, 99, 105, 116, 121, 139 or 163 between the human EPO and

cynomolgus monkey EPO are required. There is no teaching in '008 that any one of the single amino acid substitutions can be made without effecting activity. There is further evidence for the fact that Lin does not disclose EPO analogs other than human and monkey in the Federal Circuit Court of Appeal's decision of *In re Amgen* (18 USPQ2d 1610, 1991) in which they ruled that the '008 disclosure is not enabling for EPO gene analogs. The Federal Circuit Court of Appeals stated:

> *"Here, however, despite extensive statements in the specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analog genes are disclosed. Amgen argues that this is sufficient to support its claims;* ***we disagree.*** (emphasis added) (*In re Amgen* (18 USPQ2d, 1991, column 1, page 1027)

In addition, the alignment of only two species constitutes a very narrow comparison. A much more robust sequence alignment of the EPO family is presented in Figure 6 of WO 94/24160 (of record). A much different picture emerges, as to what may or may not be a non-conserved position, from the comparison of seven species in WO 94/24160 versus the two species from '008. First, at 4 positions (27, 82, 139, and 163), out of the 14 non-conserved positions between human and cynomolgus monkey, the amino acid is conserved in every species except human. Second, at 4 positions (30, 80, 104, and 116), out of the 14 non-conserved positions between human and cynomolgus monkey, the amino acid is conserved in every species except the two Macaca species. Third, at 2 positions (99 and 121), out of the 14 non-conserved positions between human and cynomolgus monkey, either the human or monkey amino acid is conserved in the other species. Forth, at 2 positions (25 and 32), out of the 14 non-conserved positions between human and cynomolgus monkey, the monkey amino acid or a single other amino acid is conserved in every species except human. Fifth, at 1 position (95), out of the 14 non-conserved positions between human and cynomolgus monkey, the human amino acid is conserved in three other species. Fifth, there are 47 additional positions, which are non-conserved between all seven of the species. The factual analysis of the larger

homology data set proves that there is not a clear teaching as to at which position to make breakpoints. The alignment of the seven species also shows there are several inconsistency between the different speculations, made by Pastan ('599), regarding the selection of breakpoints. First, Pastan on one hand suggests that glycosylation sites are good candidates for breakpoints and on the other hand non-conserved positions are good candidates. However, the potential glycosylation sites in EPO (24, 38, and 83) are conserved amongst the seven species (Figure 6 of WO 94/24160). So which suggestion is correct? Second, Pastan on one hand suggests that non-structured regions are good candidates for breakpoints and on the other hand non-conserved positions are good candidates. However, 4 positions (95, 99, 105 and 139), out of the 14 non-conserved positions between human and cynomolgus monkey, are in predicted α helical regions (page 55 of WO 94/24160). So which suggestion is correct? Third, Pastan on one hand suggests that sites at which substitutions can be made are good candidates for breakpoints and on the other hand suggests that non-structured regions are good candidates. However, in WO 94/24160 (Figure 34 and 34a) a series of amino acid substitutions were made in the predicted α helical regions which did not substantially alter the bioactivity. So which suggestion is correct? The guidelines, set forth by Pastan, for the selection of good candidates for breakpoints are not based on factual proofs. To the contrary they are only speculative and offer no guidance what so ever fit for generalization. The patentee ('599) has only listed broad and general suggestions that propose virtually ever amino acid position as a good breakpoint candidate and the skilled artisan is left to figure out for themselves what the critical parameters are.

But there are also additional deficiencies with the Office's *prima facie* case of obviousness. Pastan et al states:

> *Thus, there are two requirements for the creation of an active circularly permuted protein: 1) The* ***termini must be favorably located*** *so that the creation of the linkage does not destroy the biological activity, and 2) There must be an "opening site" where new termini can be formed* ***without disrupting a region critical for***

> ***protein folding*** *and desired activity.* (column 7, lines 13-19 emphasis added).

It is also stated in '599 that:

> *Thus, in general, good candidates for circular permutations are proteins in which the* ***termini of the original protein are in close proximity and favorably located****.* (column 7 lines 20-23 emphasis added)

Pastan et al. also states that:

> *Circular permutation requires that a protein have an opening site (i.e., between residues n and N + 1) where the formation of the termini will* ***not interrupt secondary structure crucial in the folding process or critical elements of the final conformation****. Even if the three-dimensional structure is compatible with joining the termini, it is conceivable that the kinetics and thermodynamics of folding would be greatly altered by circular permutation if opening the circularized protein separates residues that participate in short range interactions crucial for the folding mechanism or the stability of the native state. Goldenberg, Protein Eng., 7:493-495 (1989). Thus the choice of the opening site is important to the protein activity.* (paragraph bridging bottom of column 7 and top of page 8, emphasis added).

The unpredictable nature of circular permutation and the impact on protein folding has been well documented in the art. Goldenberg (1989) states:

> *However, the techniques of genetic engineering make it possible to circularly permute any DNA sequence and, therefore, any polypeptide sequence.* ***Whether the resulting protein will fold, however, is not assured****.* (page 493, column 1, 2nd paragraph, emphasis added).

Pastan et al. provides no guidance as to what the criteria are for determining if the termini of the original protein (ie. EPO) are in close proximity and favorably oriented. Pastan et al. also provides no guidance as to what the criteria are for determining what the crucial regions of EPO are for the folding process, critical elements of the final conformation or the desired actvity.

The Office has failed to establish a *prima facie* case of obviousness because it has failed to establish that the prior art teaches the requirements for proper protein folding of EPO and that the termini of EPO are in close proximity and favorably located as required by Pastan. Pastan ('599) and Lin ('008) are silent on the protein folding of EPO and the properties of the termini of EPO.

It is clear from prior art, as discussed in the present specification (pages 6-10), that the results of circular permutation have been highly variable. The totality of the prior art provides only a very limited number of examples of circular permuted proteins and the results have been variable. The primary motivation for many of these types of studies has been to study the role of short-range and long-range interactions in protein folding and stability. In many of the studies circular permutation disrupted the structure of the protein, and hence the bioactivity. The applicants point to numerous examples cited in the disclosure including; <u>*dihydrofolate reductase*</u> (Protasova et al., *Prot. Eng.* 7:1373-1377, 1995), <u>*Ribonuclease T1*</u> Garrett et al., *Protein Science* 5:204-211, 1996, <u>*omp A*</u> (Koebnik & Krämer, *J. Mol. Biol.* 250:617-626, 1995), and <u>*yeast phosphoglycerate dehydrogenase*</u> (Ritco-Vonsovici et al., *Biochemistry* 34:16543-16551, 1995) pages 6-10, of circularly permuted molecules that have significantly lowered activity, solubility or thermodynamic stability. The Examiner contends that '599 is a "**pioneering** patent, greatly advancing this art by its issuance" (page 4, line 5 of Paper No. 21 – emphasis added). However, the Federal Circuit Court has made it clear that:

> *"no objective legal test separates* ***pioneer*** *patents from non-pioneers, and it is impossible for the courts or U.S. Patent and Trademark Office to predict future of any given technology and thereby determine the*

likelihood that an invention will open new vistas of innovation" (*Augustine Medical Inc. v. Gaymar Industries Inc.* (CAFC) 50 USPQ2d 1900, emphasis added)

The Examiner contends that it is important to realize that Pastan ('599) patent was the first to **claim** circular permuteins of any protein. However, this is irrelevant because the prior art provides a number of references which describe circular permutation as far back as 1983 (Goldenberg and Creighton *J. Mol. Biol.* **165**:407-413) in which the authors describe the *in vitro* circular permutation of bovine pancreatic trypsin inhibitor and a general recombinant method to create circular permuted proteins was developed by Horlick in 1992 (Horlick et al., *Protein Eng.* **5**:427-431). The Examiner's implication that Pastan ('599) is "**pioneering**" is unfounded and improper.

The Examiner argues the state of the art is '**quite** different' between the time of Pastan's invention and the instant invention (p. 4, 1st paragraph). However, the Examiner has failed to establish that the state of the art is '**quite** different' between the time of Pastan's invention (April 8, 1994) and the instant invention (October 25, 1996). While, in addition to Pastan a few other proteins have been circularly permuted in this time period (most of which are of record) the Examiner has failed to provide factual proof regarding advances in the state of the art that would dramatically turn circular permutation into a predictable art. The required standard of reasonable expectation of success is based on experimental results, data, etc. present in the prior art. Applicants respectfully submit that the Examiner has failed to fulfill this burden to show a reasonable expectation of success. Therefore, the rationale of the present rejection is improper as an incorrect legal standard of reasonable expectation of success.

The Examiner has also improperly rejected the claims on the basis of the existence of a general method of making circular permuteins of '599, which is irrelevant as to the question whether the specific molecules would have been obvious. In re Bell, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) and In re Deuel, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995).

The file history of '599 clearly establishes that the disclosure was not enabled across the full scope of the claimed subject matter. The Examiner rejected claim 18 under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling **only** for claims limited to fusion proteins wherein the breakpoints in IL-4 (elected species) are 37/38 and 104/105 (page 5 of Paper No. 6 dated 04/04/95); in response the patentee amended claim 18 to recite that the ligand is selected from the group consisting of GM-CSF, G-CSF, IL-4 and IL-2 (Paper No. 8, dated 08/04/95); the Examiner maintained the rejection; the patentee filed a response under 37 C.F.R. § 1.116 amending claim 18 to recite only IL-4 and adding new claims reciting IL-2, G-CSF and GM-CSF in separate independent claims (Paper No. 11, dated 03/20/96); and in an interview after final the Examiner was convinced without a documented showing that IL-2 G-CSF, and GM-CSF were enabled based on gross structural similarities to IL-4. There was no evidence presented that EPO or any of the other proteins contemplated were enabled and file history clearly established the lack of enablement beyond what was claimed.

Issue 2 - Whether claims 1-4 and 6-9 are patentable under 35 U.S.C. § 103(a), over Pastan et al. (U.S. Patent 5,635,599) taken in view of Lin (U.S. 4,703,008), Chaudary et al., (1989, *Nature* 339:394-397) and Cousens et al. (U.S. Patent 4,751,180).

Chaudary *et al.* and Gearing *et al.*('180) do not suggest or provide the motivation to use the fusion protein linkers as linkers for circular permutation of EPO. The linkers of Chaudary *et al.* and Gearing *et al.*('180) are in the context of fusion proteins and the requirements of linkers for joining fusion proteins are different from the requirements of the linkers for joining the ends of circular permuted molecules. In '180 the function of the "hinge" is defined as to:

> " . . . *separate further the two fused polypeptides.*
> *Such a "hinge" would allow for steric flexibility so that the fused polypeptides would be less likely to interfere with each other, thus preventing incorrect folding* . . ." (column 4, lines 17-21).

Clearly, the purpose of the linker in the presently claimed molecules is not to separate the amino acid sequences on either side of the linker to avoid intermolecular interference of the different components of a fusion molecule which would prevent incorrect protein folding. But rather, the function is to properly position the circularly permuted sequences to allow for intramolecular interaction so that the resulting novel linear sequence can properly fold. It is also apparent that the authors of '599 were also cognoscente of the distinct functions between such, as evidenced by separate definitions for "spacer" (column 3 lines 54-61) and "linker" (column 4 lines 7-18). Chaudary *et al.* and Gearing *et al.* fail to remedy any of the deficiencies, as discussed above, of '599, Lyman, or Hannum regarding the circular permutation of EPO.

Summary

Appellants respectfully submit that in the rejection of claims 1-14 under 35 U.S.C. §103, are moot and that the law of obviousness has been misapplied. The combined teachings of references do not suggest the features of the present claims, and would not allow one of ordinary skill in the art to arrive at the present invention, especially when the patentee ('599) refutes the general applicability of circular permutation and the prior art demonstrates that the results of circular permutation is highly variable. No evidence has been presented by the Examiner demonstrating a reasonable expectation of success in connection with the present invention. At most, Pastan *et al.* (U.S. Patent 5,635,599) taken in view of Lin (U.S. 4,703,008), and in view of Chaudary *et al.* (*Nature* 339:394, 1989) and Gearing *et al.* (U.S. Patent 5,420,247) only invites one of ordinary skill to experiment with the elements disclosed therein. As pointed out above, ***obvious to try*** is an improper standard for a determination of obviousness.

Thus, a fortiori, where the very same prior art that the Examiner has relied on to try and establish a *prima facie* case of obviousness refutes the teachings that the

Examiner has depended on to establish a *prima facie* case of obviousness then it is clear that a *prima facie* case of obviousness has not been established.

For the foregoing reasons, it is respectfully submitted that the rejections of claims 1-14 were erroneous, and reversal of the decision is courteously requested.

To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Appellants request an Oral Hearing. Please charge any shortage in fees due in connection with the filing of this paper, including the extension of time fees and oral hearing request, to Deposit Account 19-1025 and please credit any excess fees to such deposit account.

Respectfully submitted,

S. Christopher Bauer
Registration No. 42,305
Telephone: 636-737-6257

Pharmacia Corporation
Corporate Patent Department
800 N. Lindberg Blvd.
Mail Zone O4E
St. Louis, MO 63167

Appendix 1

A human Erythropoietin receptor agonist polypeptide, comprising a modified Erythropoietin amino acid sequence selected from the group consisting of:

(a) the sequence of SEQ ID NO:121;

(b) a polypeptide sequence comprising residues 7-166 of SEQ ID NO:121;

(c) a polypeptide sequence comprising residues 1-161 of SEQ ID NO:121; and

(d) a polypeptide sequence comprising residues 7-161 of SEQ ID NO:121;

and wherein said modification comprises the linear rearrangement of the sequences of (a)-(d) wherein the N-terminus is joined to the C-terminus directly or through a linker capable of joining the N-terminus to the C-terminus and new C- and N-termini are created between the amino acid reside pairs of SEQ ID NO:121 selected from the group consisting of:

23-24, 24-25, 25-26, 26-27, 27-28, 28-29, 29-30, 30-31, 31-32, 32-33, 33-34, 34-35, 35-36, 36-37, 37-38, 38-39, 40-41, 41-42, 43-44, 44-45, 45-46, 46-47, 47-48, 48-49, 50-51, 51-52, 52-53, 53-54, 54-55, 55-56, 56-57, 57-58, 77-78, 78-79, 79-80, 80-81, 81-82, 82-83, 84-85, 95-86, 86-87, 87-88, 88-89, 108-109, 109-110, 110-111, 111-112, 112-113, 113-114, 114-115, 115-116, 116-117, 117-118, 118-119, 119-120, 120-121, 121-122, 122-123, 123-124, 124-125, 125-126, 126-127, 127-128, 128-129, 129-130, 130-131, and 131-132; and

wherein said Erythropoietin receptor agonist polypeptide may optionally be immediately preceded by (methionine^{-1}), (alanine^{-1}) or (methionine^{-2}, alanine^{-1}).

2. The Erythropoietin receptor agonist polypeptide, as recited in claim 1, wherein said linker is selected from the group consisting of;

GlyGlyGlySer SEQ ID NO:123;
GlyGlyGlySerGlyGlyGlySer SEQ ID NO:124;
GlyGlyGlySerGlyGlyGlySerGlyGlyGlySer SEQ ID NO:125;
SerGlyGlySerGlyGlySer SEQ ID NO:126;
GluPheGlyAsnMet SEQ ID NO:127;
GluPheGlyGlyAsnMet SEQ ID NO:128;
GluPheGlyGlyAsnGlyGlyAsnMet SEQ ID NO:129; and
GlyGlySerAspMetAlaGly SEQ ID NO:130.

3. The Erythropoietin receptor agonist polypeptide of claim 1 selected from the group consisting of;
SEQ ID NO:1; SEQ ID NO:2; SEQ ID NO:3; SEQ ID NO:4; SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:8; SEQ ID NO:9; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:12; SEQ ID NO:13; SEQ ID NO:14; SEQ ID NO:15; SEQ ID NO:16; SEQ ID NO:17; SEQ ID NO:18; SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:22; SEQ ID NO:23; SEQ ID NO:24; SEQ ID NO:25; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:29; SEQ ID NO:30; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; SEQ ID NO:40; SEQ ID NO:41; SEQ ID NO:42; SEQ ID NO:43; SEQ ID NO:44; SEQ ID NO:45; SEQ ID NO:46; SEQ ID NO:47; SEQ ID NO:48; SEQ ID NO:49; SEQ ID NO:50; SEQ ID NO:51; SEQ ID NO:52; SEQ ID NO:53; SEQ ID NO:54; SEQ ID NO:55; SEQ ID NO:56; SEQ ID NO:57; SEQ ID NO:58; SEQ ID NO:59 and SEQ ID NO:122.

4. The Erythropoietin receptor agonist polypeptide of claim 3 wherein the linker sequence is selected from the group consisting of;

GlyGlyGlySerGlyGlyGlySer SEQ ID NO:124;
GlyGlyGlySerGlyGlyGlySerGlyGlyGlySer SEQ ID NO:125;
SerGlyGlySerGlyGlySer SEQ ID NO:126;
GluPheGlyAsnMet SEQ ID NO:127;
GluPheGlyGlyAsnMet SEQ ID NO:128;
GluPheGlyGlyAsnGlyGlyAsnMet SEQ ID NO:129; and
GlyGlySerAspMetAlaGly SEQ ID NO:130.

5. A nucleic acid molecule comprising a DNA sequence encoding the Erythropoietin receptor agonist polypeptide of claim 1.

6. A nucleic acid molecule comprising a DNA sequence encoding the Erythropoietin receptor agonist polypeptide of claim 2.

7. A nucleic acid molecule comprising a DNA sequence encoding the Erythropoietin receptor agonist polypeptide of claim 3.

8. A nucleic acid molecule comprising a DNA sequence encoding the Erythropoietin receptor agonist polypeptide of claim 3 selected from the group consisting of;
SEQ ID NO:60; SEQ ID NO:61; SEQ ID NO:62; SEQ ID NO:63; SEQ ID NO:64; SEQ ID NO:65; SEQ ID NO:66; SEQ ID NO:67; SEQ ID NO:68; SEQ ID NO:69; SEQ ID NO:70; SEQ ID NO:71; SEQ ID NO:72; SEQ ID NO:73; SEQ ID NO:74; SEQ ID NO:75; SEQ ID NO:76; SEQ ID NO:77; SEQ ID NO:78; SEQ ID NO:79; SEQ ID NO:80; SEQ ID NO:81; SEQ ID NO:82; SEQ ID NO:83; SEQ ID NO:84; SEQ ID NO:85; SEQ ID NO:86; SEQ ID NO:87; SEQ ID NO:88; SEQ ID NO:89; SEQ ID NO:90; SEQ ID NO:91; SEQ ID NO:92; SEQ ID NO:93; SEQ ID NO:94; SEQ ID NO:95; SEQ ID

NO:96; SEQ ID NO:97; SEQ ID NO:98; SEQ ID NO:99; SEQ ID NO:100; SEQ ID NO:101; SEQ ID NO:102; SEQ ID NO:103; SEQ ID NO:104; SEQ ID NO:105; SEQ ID NO:106; SEQ ID NO:107; SEQ ID NO:108; SEQ ID NO:109; SEQ ID NO:110; SEQ ID NO:111; SEQ ID NO:112; SEQ ID NO:113; SEQ ID NO:114; SEQ ID NO:115; SEQ ID NO:116; SEQ ID NO:117; SEQ ID NO:118 and SEQ ID NO:119.

9. A nucleic acid molecule comprising a DNA sequence encoding the Erythropoietin receptor agonist polypeptide of claim 4.

10. A method of producing a Erythropoietin receptor agonist polypeptide comprising: growing under suitable nutrient conditions, a host cell transformed or transfected with a replicable vector comprising said nucleic acid molecule of claim 5, 6, 7, 8 or 9 in a manner allowing expression of said Erythropoietin receptor agonist polypeptide and recovering said Erythropoietin receptor agonist polypeptide.

11. A composition comprising; a Erythropoietin receptor agonist polypeptide according to claim 1, 2, 3 or 4; and a pharmaceutically acceptable carrier.

12. A composition comprising; a Erythropoietin receptor agonist polypeptide according to claim 1, 2, 3 or 4; a second protein; and a pharmaceutically acceptable carrier.

13. The composition of claim 12 wherein said second protein is selected from the group consisting of: GM-CSF, G-CSF, c-mpl ligand, M-CSF, IL-1, IL-4, IL-2, IL-3, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, LIF, flt3/flk2 ligand, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor, stem cell factor, IL-3 variant,

fusion protein, G-CSF receptor agonist, c-mpl receptor agonist, IL-3 receptor agonist, and multi-functional receptor agonist.

14. A method of stimulating the production of hematopoietic cells in a patient comprising the step of; administering a Erythropoietin receptor agonist polypeptide of claim 1, 2, 3 or 4, to said patient.